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Comprehensive Training Design for CRAs and CRCs

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Multiple trends within medical device and pharmaceutical trials have led to a sharp rise in demand for knowledgeable and well trained Clinical Research Associates (CRAs/monitors) and Clinical Research Coordinators (CRCs). Career opportunities for clinical research personnel are expected to continue increasing for the foreseeable future. In addition, the global clinical trials market is projected to experience annual growth (CAGR) of 4.5% between 2018 and 2023 (1). At the same time, rising trial costs for sponsors have resulted in mounting pressure to rapidly complete clinical studies. In order to maintain human subject protection and data integrity under expedited study timelines, sites and sponsors must rely on skilled CRAs and CRCs. The lack of formal training and on-boarding programs for CRAs and CRCs has played a significant role in the current shortage of qualified workers. Training programs are needed to ensure that workforce resources are sufficient to support future product development.

Training programs should build proficiency in core job skills and be based on a strong regulatory foundation. Course curriculum should include practicum/on-the job training as well as exposure to emerging topics such as future trends in clinical data and patient centricity. As trials continue to become more complex, CRAs and CRCs will need to be able to manage new technology and evolving job responsibilities. Training programs must be flexible enough to adapt to changes in the industry while also maintaining a robust regulatory framework.

The following curriculum components are recommended for use in the development of a comprehensive training program for CRAs and CRCs:

1. Regulation Based:

Both Sites and Sponsor personnel must have a clear understanding of the rules and requirements of clinical trial conduct. Compliance in drug and device studies can be assessed based on four principle areas (2):

F	Federal regulations • Is it specified in 21 CFR Parts 11, 50, 54, 56, 312, or 812?
A	Agreements • Is it a requirement in the Agreement?
I	Investigational Plan • Is it a requirement in the investigational plan (protocol)?
R	Requirements of the IRB • Is it a requirement of the IRB?

F Federal Regulations: 21 CFR Parts 11, 50, 54, 56, 312, and 812

Course Instruction: Present 21 CFR regulations and provide an in-depth explanation of parts 11, 50, 54, 56, 312, and 812; include interpretation and application of regulations to a clinical study setting. The paper or electronic version of 21 CFR should be provided to trainees.

Training Objective: Ability to identify areas covered by 21 CFR Parts 11, 50, 54, 56, 312, and 812 and ability to reference specific requirements. Trainees should be able to explain how compliance with various parts of 21 CFR is documented through site files and/or assessed during monitoring visits.

A Agreements: FDA Form 1572 – Drugs/ Investigator Agreements – Devices

Course Instruction: Provide specifics of the requirements typically contained in the Investigator Agreement and FDA Form 1572; explain who completes the forms, timeline for completion, who is responsible for maintaining the document, and when the document is reviewed during monitoring visits.

Training Objective: Identify the conditions that Investigators agree to by signing the Investigator Agreement / FDA Form 1572. Describe details regarding completion, maintenance, and verification.

I Investigational Plan: Protocol

Course Instruction: Explain the purpose of the protocol and review individual sections. Emphasize the protocol sections most often referenced in both conduct and monitoring of trials (i.e., eligibility criteria, schedule of events, primary end point(s), protocol deviations, adverse events, study risks, etc.). Provide an in-depth explanation of protocol deviation and adverse event tracking and reporting.

Training Objective: Explain the purpose of individual protocol sections and identify those sections that should be carefully reviewed for conducting and monitoring trials. Identify unique or challenging aspects of the protocol (e.g., non-standard of care testing, expedited adverse event reporting, blinding and/or randomization procedures) that may put clinical sites at risk for low site compliance. Describe the process for tracking and reporting adverse events and protocol deviations.

R Requirements of the IRB

Course Instruction: Detail the function and composition of IRBs, the process for submissions and approvals, continuing review, specifics of reporting requirements, the role of central and local IRBs, and how to access IRB policies and procedures.

Training Objective: Explain the submission and approval process and describe requirements for continuing review, explain how to ensure compliance with IRB policies and procedures, identify the differences between central and local IRBs, and specify how to ensure adequate reporting of noncompliance.

2. FDA Inspection Awareness and Preparation

The table below lists the most common citations observed during FDA Clinical Investigator and Sponsor/ Monitor/ CRO Inspections in 2017 (3). The findings below have been among the most frequently cited in FDA inspections since 2012. It is important to provide both Sponsors and Site personnel with targeted training in these areas in order to mitigate the risk of future noncompliance.

FDA Clinical Investigator Inspection Common Citations (2017)		
CITATION	TARGETED CRC TRAINING	TARGETED CRA TRAINING
Failure to follow the investigational plan/agreement or regulations	Regulation based training (Refer to Item 1 above) Institution-specific training	Regulation based training (Refer to Item 1 above)
Protocol deviations	Understanding how to review protocols for noncompliance risk areas, understanding what constitutes a 'deviation', how to avoid deviations as a CRC, ensuring timely tracking and reporting, how to correct and prevent deviations. Familiarity with Institution-specific and Sponsor requirements for protocol deviation reporting.	Tracking and reporting, securing compliance at sites, awareness of frequent deviations, instruction on correction and prevention of deviations
Inadequate recordkeeping	Understanding the institution's source documentation (EMR, research charts, etc.), completion of source and study documentation, maintenance of records, signature and dating of documents, ICH GCP training	Understanding what constitutes as source (4), how to verify with the "right" source, maintenance of records, signature and dating of documents, ICH GCP)training, securing compliance with complete and current record-keeping
Inadequate subject protection – informed consent issues, failure to report AEs	Understanding of institution/IRB Informed consent process and documentation, HIPAA requirements, LAR and witness signature, short form or alternative language consent, re-consent, vulnerable populations, other miscellaneous requirements	Understanding regulatory requirements for the informed consent process and documentation, monitoring informed consent and common mistakes, LAR and witness signature, use of short form or alternative language consent, determining when re-consent is required, vulnerable populations, HIPAA, tracking and verifying various site IRB policies on informed consent
Inadequate accountability for the investigational product	Investigational Product documentation, protocol/product-specific labeling, ordering, receipt, use, IFU and IB, storage, access, returns, disposal, destruction, and final disposition	Investigational Product documentation, labeling, ordering, receipt, use, IFU and IB, storage, access, returns, disposal, destruction, and final disposition, verifying and documenting accountability during monitoring visits
Inadequate communication with the IRB	Regulation based training (Refer to Item 1 above)	Regulation based training (Refer to Item 1 above)

FDA Sponsor/Monitor/CRO Inspection Common Citations (2017)		
CITATION	CRC TRAINING	CRA TRAINING
Inadequate monitoring	Emphasis of site responsibility for study conduct and compliance with regulations, training on developing collaborative relationship with CRA to achieve compliance while not relying on the CRA to ensure that the site is following applicable regulations	Monitoring plan adherence, source document verification, regulatory review, methods to secure compliance, training on developing collaborative relationship with site to achieve compliance, risk-based and remote monitoring, proper escalation and documentation of study issues
Failure to bring investigators into compliance	As detailed in inadequate monitoring above	As detailed in inadequate monitoring above
Inadequate accountability for the investigational product	As detailed in inadequate accountability for the investigational product above	As detailed in inadequate accountability for the investigational product above
Failure to obtain FDA and/or IRB approval prior to study initiation	Review approvals needed prior to starting trial, regulatory document checklist, amendment process and approvals, trial changes that need to be reported to IRB and/or FDA	Review approvals needed prior to starting trial, site-completed documents needed prior to start-up, amendment process and approvals, trial changes that need to be reported to IRB and/or FDA

3. Role in Ensuring Patient Safety and Data Integrity

CRAs and CRCs should be taught the importance of their role in protecting the rights, safety, and well-being of human subjects and ensuring the integrity of trial data. This responsibility should be emphasized as a critical piece of the device and drug development process.

Training should include a review of major historical events that have shaped trial conduct and regulations (5) (e.g., Tuskegee Study, Food, Drug, and Cosmetic Act, Nuremberg Trials, Declaration of Helsinki, Belmont Report, International Conference on Harmonization (ICH), Common Rule, Good Clinical Practice, etc.).

Clinical trial history can be useful in understanding the basis for current regulations and is designed to build commitment to protecting subject safety and data integrity.

4. Practicum/ On-The-Job Training

Performing Monitoring Visits and Site Communication (CRAs)

CRAs should be given in-depth instruction on the conduct of periodic monitoring visits, site initiation visits, close-out visits, site assessment visits, investigator meetings, and remote monitoring visits. Trainees should shadow experienced personnel on each type of visit until performance is adequate. After establishing competence, studies of increasingly complexity and clinical sites with poor compliance patterns should be integrated.

CRAs must be able to effectively communicate with clinical site staff, both on-site and remotely. Interactions should be treated as collaborative rather than punitive and the principal goal of securing compliance should always remain at the forefront. Trainees should observe written and verbal communication between experienced CRAs and investigative sites.

Subject Visits and Sponsor Communication (CRCs)

CRCs should be trained on subject recruitment, informed consent and screening, enrollment and randomization, scheduled follow-up, unscheduled follow-up, early termination, lost-to-follow-up, and study exit. Research coordinators should shadow experienced site members on each type of visit until competence is established.

Effective communication with the sponsor (or CRO if applicable) is essential to the daily work of research coordinators. Communication should always be professional and CRCs should treat sponsors as partners in achieving compliance. It is important to emphasize that the goal of both sites and sponsors is to run an effective, safe, and compliant study. Trainees should witness written and verbal communication between more experienced CRCs and CRAs/clinical project managers/sponsor representatives.

Report Writing (CRAs)

Monitoring reports should be clear and concise, while also containing sufficient supporting detail. Trainees should review well-written reports and follow-up letters from multiple types of visits and report templates in order to become comfortable with the skill-set. The new CRAs should assist in the report writing process when possible (6).

Study Records (CRCs)

Study records should be maintained in accordance with GCP ALCOA. New CRCs should complete GCP training and review examples of study records (subject specific and regulatory) that were completed in accordance with GCP ALCOA; common documentation deficiencies should also be reviewed. Training should emphasize the need for study documents to demonstrate Investigator oversight of trial conduct and subject safety. CRCs should also be familiar with required regulatory documents and the process for submitting new studies and amendments to the IRB.

5. Emerging Topics

Developments in the industry that impact the jobs of CRAs and CRCs should be incorporated into training programs. Recent trends include the growing use of Real World Evidence (RWE) and the rise in patient centricity.

RWE is data obtained directly from patients via health tracking devices, wearable monitors, social media, and other mobile devices. This data is obtained from subjects in real-time and is used to provide clinicians with an immediate assessment of outcome data. CRCs will need to become familiar with RWE systems in order to ensure compliant Subject use and proper device functioning. Subjects will need to be taught how to wear, transmit (if needed), and store the device as well as the requirements for study compliance. CRAs will need to be able to monitor RWE data and navigate multiple software and hardware platforms.

RWE is a component of the increasingly patient-centered nature of trials. The growing use of social media, study websites, and mobile apps has given subjects additional options for finding and engaging with clinical trials. Research professionals will need to place greater emphasis on patient perspective when designing and conducting trials. Subjects should feel that they are partnering with sites in finding new treatments rather than serving as passive participants. Patient centricity may increase the need for recruitment/retention campaigns as Subjects will have additional options for trial selection and engagement.

6. Training Records

All training activities must be documented to be considered complete. Training records should, at a minimum, include the training topic/lesson content, the version of the training material, the date the training was completed, the trainer's name/credentials and signature, and the trainee's name/credentials and signature. Completed records should be maintained in a secure system that is accessible to the trainee and authorized colleagues.

Conclusion

Multiple developments within the clinical trials industry have led to an increase in demand for well trained and knowledgeable CRAs and CRCs. Innovative training programs are needed to ensure that the workforce is able to support the continued development of new devices and drugs. Multiple curriculum components are recommended for integration into a comprehensive training design.

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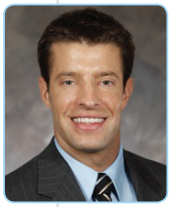

Since joining IMARC in May, 2013 Paul has monitored and audited studies investigating treatments for thoracic aneurysms, aortic dissection and transection, urinary incontinence, intracranial aneurysms, and robotic devices for percutaneous coronary intervention. His diverse background in surveillance, biostatistics, and site level roles creates a unique perspective on monitoring and auditing clinical trials. He is able to balance the regulatory-based nature of the job with the need to serve as both a collaborator and advisor for sites, CROs, and sponsors. Paul follows an upstream prevention model in his work in which he strives to identify, correct, and prevent potential issues before they become problems.

Paul has earned CCRA credentials through the Association of Clinical Research Professionals. He received his Master of Public Health from The Rollins School of Public Health at Emory University and his Bachelor of Arts degree in psychology from The University of Michigan.

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